Grant # DA16511

Center Director: Kathleen T. Brady, M.D., Ph.D.

Overview

The common thread that ties the projects of this SCOR together is relapse to drug abuse. MUSC has demonstrated a long-standing interest in substance abuse research as is clearly evidenced by strength in both basic science and clinical research in this area. Importantly, the proposed investigative team has experience in conducting translational research in an NIAAA-funded center initiative since 1996. While our track record in research and clinical efforts in substance abuse is strong, MUSC does not presently have the same strength in women's health initiatives. The SCOR would provide a catalyst to growth in this area.

In developing the SCOR application, we gathered individuals with a unique blend of expertise from across campus. The interdisciplinary and cross-college nature of this initiative should ensure the sharing of ideas from multiple perspectives and guarantee that the SCOR has maximum impact on research and the general culture within MUSC.
Specific Aims of the MUSC SCOR:
Specific Aim #1: To set the occasion for focused, coordinated, integrated and unified efforts along a single program of gender-related research in substance use disorders at MUSC.
Specific Aim #2: To build an infrastructure to encourage and support gender-based research growth throughout the campus.
Specific Aim #3: To attract trainees and new faculty to the area of research, particularly patient-oriented research, in women's health issues.
Specific Aim #4: To centralize various individual research efforts currently underway, as well as those proposed in the SCOR.

There are a total of four research components. All are focused on gender issues in relapse to substance use disorders. However, the varied investigations range from an exploration of sex differences in response to pharmacologic agents to investigations of gender differences in drug reinstatement in rodents, craving in humans and gender-specific treatment paradigms.

Component #1: Sex Differences in an Animal Model of Relapse: Dr. Ronald See, an experienced pharmacologist, will be exploring gender differences in several well-developed animal models of drug self-administration reinstatement.
Component #2: Gender Differences in Response to Cues in Cocaine Dependence: Dr. Kathleen Brady will lead this study of gender differences in response to cocaine-related cues and negative emotional states in men and women. This study will take place in the GCRC and involves the measurement of HPA axis response as well as autonomic and subjective response.

Component #3: Gender, Menstrual Cycle and Smoking Cue Reactivity: Dr. Himanshu Upadhyaya will conduct a project studying the effect of menstrual cycle on the reactivity to nicotine and negative affect cues in humans.
Component #4: Gender Influence on Preclinical Alcohol Pharmacology: Dr. Larry Middaugh will be using a rodent model to investigate the impact of gender and estrus state on the rewarding effects of ethanol and ethanol-conditioned stimuli.

This is an opportune time to develop a focused effort on research in women's health at MUSC. In terms of the thematic focus of the proposed SCOR, there is a convergence of opportunities and expertise in translational research in neuroscience and addiction. A cadre of talented and experienced basic scientists and clinical researchers from throughout MUSC interested in the SCOR has emerged and interdisciplinary collaboration and communication has been established. There is strong support from the leadership of MUSC. The focus on women's health and substance use disorders is sorely needed and complements many of the ongoing University efforts. Thus, the timing and thematic focus seem to ideally support the development of a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health at MUSC.

Principal Investigator: **Ronald See, Ph.D.**

Project 1: Sex Differences in an Animal Model of Relapse

Strong evidence suggests that gender differences exist in drug abuse and dependence. Relapse to drug abuse following prolonged abstinence is a significant impediment in the long-term treatment of drug dependence. Although multiple factors have been identified in relapse, there remains a lack of understanding of the role of sex differences in the process of relapse following withdrawal from chronic drug self-administration. Craving states produced by conditioned-cues, stress, and drugs themselves, are all believed to be critically involved in relapse to compulsive drug-seeking behavior. Reinstatement of extinguished operant responding is a well-established animal model of relapse that has clinical relevancy. In this model, three experimental paradigms allow for the reinstatement of drug-seeking behavior (as measured by operant responding on a previously drug-paired lever) to levels that approximate those seen during primary reinforcement. The three models include a) re-exposure to discrete stimuli (tone+light) previously paired with cocaine infusions; b) exposure to brief stress (footshock); and c) noncontingent administration of cocaine itself. In this project, studies are proposed to examine sex differences in these various forms of reinstatement and to test the general hypothesis that female and male rats are uniquely susceptible to the different forms of reinstatement. Furthermore, we will establish the degree to which selective pharmacological compounds will differentially attenuate reinstatement in females vs. males. These experiments provide an integrated approach to understanding sex differences in relapse to cocaine-seeking behavior. Information gained from this project will also provide direction for other components of the SCOR and help direct the future development of gender-specific treatments for craving and relapse.

Principal Investigator: Kathleen T. Brady, M.D., Ph.D.

Project 2: Gender Difference in Response to Cues in Cocaine Dependence

A critical area in the investigation of gender differences in cocaine dependence is differences in factors influencing initiation, maintenance and relapse to drug use. Human laboratory studies indicate that both cocaine-related cues and negative emotional stimuli can elicit craving in cocaine-dependent individuals. There is some evidence to suggest that this effect may be more robust in women as compared to men. Animal studies have clearly demonstrated that exposure to stress facilitates both the initiation and reinstatement of substance use in previously dependent animals. The hypothalamic-pituitary-adrenal (HPA) axis, one of the most important hormonal systems involved in the stress response, is likely to be an important mediator of stress-facilitated drug self-ad ministration. Of particular relevance to this proposal, there are important gender differences in the response of the HPA axis to stress. Preliminary data from our group suggest gender differences in the biologic and subjective response to these different types of stressors. In this proposed study, we plan to build upon these intriguing findings. Specifically HPA axis (e.g., ACTH, cortisol), physiologic (e.g., HR, GSR) and subjective response to the presentation of cocaine-related cues and negative affect-inducing cues will be compared in cocaine dependent men, women and matched control groups without cocaine dependence. A CRH stimulation test will also be performed. Following the test procedures, individuals will return for a follow-up visit at one week and one month to assess the amount and subjective attributions of drug use. In summary, this project is designed to build upon our ongoing research in the area of stress reactivity and substance use disorders. Specifically, this study will complement Project 1, which focuses on gender differences in animal models of reinstatement and will focus on gender differences in response to differing stimuli associated with relapse. Exploration of potential neurobiologic underpinnings of gender differences in precipitants relapse to drug use can have important implications for prevention and treatment.

Principal Investigator: Himanshu P. Upadhyaya, M.D.

Project 3: Gender, Menstrual Cycle and Smoking Cue Reactivity

Cigarette smoking is common; approximately 25% of adults over 18 years of age are regular smokers. Craving is an important component of the symptoms experienced during smoking cessation and it considered a crucial factor in relapse. There is some evidence that menstrual cycle may impact smoking and relapse for women, but this has not been well explored. Hence, menstrual cycle phase may be an important modulator of craving and may contribute in relapse among women attempting smoking cessation. There is also data suggesting that there are different subjective and physiological responses to nicotine during different phases of the menstrual cycle, but little work has been done in exploring the effect of menstrual cycle phases on smoking cue-reactivity. Research on the effect of menstrual cycle phase on smoking cue-reactivity may be especially important for smoking cessation treatment as it is common practice in smoking cessation programs to set a quit date prior to the quit attempt. Knowledge about the menstrual cycle phase differences in cue-reactivity may help in setting an optimal quit date for women in order to maximize the chances of successful smoking cessation. The specific aims of the proposed project are: 1. To examine the effect of menstrual cycle phase on reactivity to "in vivo" cigarette smoking cues and negative affect-inducing cues in nicotine-dependent women. 2. To examine gender differences in the reactivity to "in vivo" cigarette smoking cues and negative-affect inducing cues in nicotine-dependent men and women. The proposed project will use both in vivo smoking cues, as well as negative affect/stress cues to explore smoking cue-reactivity in female smokers during four biologically verified menstrual phases. Female cigarette smokers' reactivity will also be compared to the reactivity of male cigarette smokers who will be tested in a similar protocol. Both subjective craving and mood responses, as well as physiological responses (e.g., real-time heart rate, galvanic skin conductance) will be measured during the study. This information may help in designing specific smoking-cessation approaches for nicotine-dependent women.

Principal Investigator: Lawrence D. Middaugh, Ph.D.

Project 4: Gender Influence on Preclinical Alcohol Pharmacology

The proposed experiments utilize a C5713L/6 (B6) murine model to determine if gender and/or estrus state influence the response to ethanol and ethanol conditioned stimuli or influence the impact of potential therapeutic agents on the response to ethanol-related stimuli. Although both positive and negative reinforcing stimuli regulate behavior directed toward obtaining and consuming ethanol and other abused drugs, we focus on evaluating the influence of gender on the effect on the positive reinforcing stimuli related to ethanol. Such information is basic and applicable to conditions reflective of "craving", "loss of control", or "relapse after abstinence", all of which have ethanol-related stimuli as a component. Although female members of our society contribute to the alcoholic population, preclinical investigations on potential therapeutic agents focus almost exclusively on young male rats. The general hypothesis guiding the proposed research is that gender and estrus state will (1) influence the rewarding effects of ethanol and ethanol -conditioned stimuli and (2) influence the ability of potential therapeutic agents to reduce the reward value of these stimuli. The strategy for testing this hypothesis is to compare the impact of ethanol-related stimuli in male and female mice as well as female mice during two distinct stages of estrus. The effect of estrus cycle on the effect of potential therapeutic agents (Naltrexone, Onclansetron, Vigabatrin) will be measured using behavioral evaluations of the rewarding effects of ethanol and ethanol-conditioned stimuli. Opioid antagonists (Naltrexone) 5-HT3 antagonists (Ondansetron) and GABA transaminase inhibitors (Vigabatrin) have all been shown to attenuate the rewarding effects of ethanol in male monkeys, rats, and mice and can also reduce the rewarding effects of ethanol-conditioned stimuli in male rats and mice. Whether effects on female members of the different species follow those noted for males is unknown, and is the focus of this proposal. An important aspect of the proposed work is to establish whether the drugs can attenuate the rewarding effects of ethanol and ethanol-conditioned stimuli with few unwanted side effects in female mice as we have demonstrated for male mice. Although the experiments are for ethanol reward, they should be generalized to treatment in paradigms for other drugs of abuse such as cocaine, heroin and morphine.